ATTACHMENT B

REMARKS

By the present amendment, Claims 1 and 23 have been amended so as to further point out the patentable subject matter of the present invention and more clearly show that these claims are directed to subject matter that is not disclosed or suggested in the prior art. In addition, other minor amendments have been made to be consistent with the language of Claims 1 and 23 and to make certain changes suggested by the Examiner to clarify the language of the claims. In particular, Claims 1 and 23 have been amended so as to reflect that the monoclonal antibodies of the present invention are capable of inhibiting collagen binding to *S. aureus*, which is disclosed throughout the application, e.g., at page 1, first paragraph. Accordingly, the present amendments add no new matter to the present application. As a result of the present amendments, Claims 1, 13 and 23 have been amended, and Claims 10, 12, and 26 are canceled without prejudice. In short, for reasons as stated below, no reference wither singly or in combination discloses or suggests a monoclonal antibody in accordance with the claims of the present application, and the Examiner's rejections on the basis of the prior art should be withdrawn.

In particular, the present invention as now embodied in Claims 1 and 23 and their dependent claims, provides a monoclonal antibody which is capable of displacing *S. aureus* bacteria which has been previously bound to collagen. Contrary to the Examiner's presumptions, and as shown below, the ability to achieve displacement of *S. aureus* from collagen has been recognized as "remarkable" in journal articles discussing these results, and is a totally unexpected behavior which is **not** correlated to the inhibition of collagen binding to *S. aureus* as the Examiner has incorrectly presumed.

The invention as reflected in the present claims is thus completely novel and unobvious over any of the prior art references citing other proteins or regions from the collagen binding protein which do **not** have those properties.

In this regard, the Examiner's attention is drawn to the journal article attached hereto as Appendix A of Visai et al., Journal of Biological Chemistry, 275 (51):39837-39845 (Dec. 2000) which discusses the experiments regarding the displacement ability of monoclonal antibodies to the CNA 151-318 region. Importantly, among the unexpected findings of these studies were the ability of these antibodies to displace *S. aureus* from collagen which was totally unexpected and remarkable, in particular because there was **no correlation** between the inhibition of collagen and displacement behavior (see, e.g., p. 39841, left side bottom, "some goods inhibitors were poor displacers"). Another finding was that certain monoclonal antibodies to other regions which encompassed the 51-318 could not inhibit collagen binding to *S. aureus* **or** displace bacteria previously bound to collagen (see, e.g., p. 39842, right side, mAb 16H9 raised against 30-531 region "did not inhibit binding of 125I-collagen to bacteria" and was "essentially inactive in the detachment assay", i.e., unable to displace S. aureus previously bound to collagen). Accordingly, the main presumptions of the Examiner, namely that an antibody shown to inhibit bacteria attachment to collagen inherently displaces that bacteria when previously bound, and that an antibody to a larger region encompassing a smaller region would inherently have the same properties as that smaller region, are simply untrue.

An additional Appendix is attached which provides further evidence showing that the central assumption of the Examiner, namely that the antibodies to a larger region will have the same properties as antibodies to the smaller region and automatically recognize that smaller region, is again untrue. In particular, as shown in Appendix B, monoclonal

antibodies generated to various regions of the CNA binding protein had starkly different results in that many of the antibodies did not recognize other binding regions, even when that region was encompass by the region that the antibody was generated against. For example, mAb to the CBD region 61-343 did **not recognize any other region**, including the **lesser included regions** such as the present region 151-318 or the region 151-297 (which was also not recognized by an mAb to the region 30-531). Thus, it is **not** the case that a monoclonal antibody to a larger region of the collagen binding protein inherently will recognize a lesser- included region, and indeed this is often not the case. Accordingly, the materials attached hereto, as explained further below, make it clear that the presently claimed invention is not disclosed or suggested in the prior art references, and indeed obtains unexpected and remarkable beneficial results not previously contemplated in the prior art.

In the Official Action, the Examiner rejected the claims under the judicially created doctrine of obviousness on the basis of copending application 09/813,820. In particular, the Examiner stated that monoclonal and polyclonal antibodies binding to amino acids 61-343 of the CNA peptide "read on" the present claims because such antibodies would "also bind to a smaller CNA peptide that contains amino acids 151-318." See Official Action, Page 3. Such a statement is untrue as shown in Appendix B wherein the monoclonal antibodies to 61-343 **did not recognize** the region CNA 19, amino acids 151-318. Moreover, the other required properties of the present claims, including the ability to displace *S. aureus* from collagen is **not** shown or suggested in the copending application since displacement has been shown to be a property which does **not** correlate with an antibody's ability to inhibit collagen binding. It is clear that the monoclonal antibodies as claimed in the present application are not disclosed or

claimed in the copending application 09/813,820 and indeed achieve unexpected remarkable and beneficial properties not contemplated in the prior art .

In the Official Action, the Examiner rejected the claims under the judicially created doctrine of obviousness-type double patenting over claims 1-12 of U.S. Pat. No. 6,288,214, and also rejected the claims under 35 U.S.C. § 103(a) as being obvious over U.S. Pat. No. 6,288,214. In addition, the Examiner rejected the claims under 35 U.S.C. 102(e) on the basis of U.S. Pat. No. 6,288,214. In all cases, essential to the Examiner's rejections was the argument that the ability of an antibody to inhibit bacterial adhesion to collagen was directly related to an ability to displace the bacteria to collagen and the argument that antibodies to a larger region inherently have the same properties as antibodies to a lesser-included region. As shown in the attachments and as described above, these presumptions simply are not true.

In particular, as expressed in the Visai article attached hereto as Appendix A, it was shown unexpectedly that certain monoclonal antibodies had the ability to displace *S. aureus* from collagen, but moreover that there was **no correlation** between the inhibition of collagen and displacement behavior (see, e.g., p. 39841, left side bottom, "some goods inhibitors were poor displacers"). Accordingly, the Examiner was incorrect in the argument that the ability to inhibit the binding of S. aureus to collagen had any correlation with an antibodies ability to displace bacteria when already bound to collagen.

More importantly, the Examiner has presumed that antibodies to a region on the collagen binding protein inherently maintain all of the properties of antibodies to a lesser-included region, and this is simply untrue. Once again, as shown in Visai, a monoclonal antibody generated against the 30-531 region was **quite different** than the monoclonal antibody generated against the 151-318 region, in particular in that is **did not** show any

displacement behavior and moreover did **not** inhibit the binding of *S. aureus* to collagen. In particular, as shown in Visai, the mAb 16H9 raised against 30-531 region "did not inhibit binding of 125I-collagen to bacteria" and was "essentially inactive in the detachment assay", i.e., it was **not** capable of displacing *S. aureus* previously bound to collagen. These findings with regard to recognition and properties are not surprising since, as Applicants have already shown on the record that monoclonals are generated from specific epitopes, and a monoclonal generated again a larger region may indeed recognize an epitope outside of the lesser-included region. Moreover, because such monoclonal antibodies may be differently sized that monoclonals to lesser-included regions, they may have different shapes and configurations, and thus be quite different in properties. This is confirmed in that monoclonals generated against 30-531 had vastly different properties than the claimed monoclonals to the 151-318 region, and indeed the 30-531 antibodies were **not** capable of displacing *s. aureus* bound to collagen as do the monoclonals of the claimed invention.

Thus, the presently claimed invention is clearly not disclosed or suggested by Hook U.S. Pat. No. 6,288,214, and indeed obtains significant and unexpected benefits in displacement which were not contemplated or suggested in the prior art. Accordingly, the Examiner's rejection on the basis of this patent is respectfully traversed and should be withdrawn.

Finally, the Examiner has rejected the claims on the basis of Hook International application WO 97/43314 which is based on the same priority document upon which U.S. Pat. No. 6,288,214 was based, as well as copending application 09//813,820 which is a child application of the application which became the '214 patent, and this all of the arguments as stated above clearly apply to the Examiner's rejection on the basis of WO

97/43314. Moreover, once again, the Examiner's rejection relies on assumptions that are not true, namely the Examiner's argument that "the antibodies have been shown to inhibit collagen binding to CBP and *S. aureus* . . . Hence the antibodies displace *S. aureus* bound to collagen." See Official Action, at Page 8. As shown above, this is simply not the case, and there is no correlation between inhibition and displacement. Indeed, the monoclonal to the greater region 30-531 was unable to displace bacteria from bound collagen unlike the monoclonal antibodies of the presently claimed invention. In short, the prior Hook patent references including WO 97/43314 failed to disclose or suggest the monoclonal antibody of the present invention, namely a cross-reactive monoclonal that recognizes the 151-318 and is capable of both inhibiting the binding of *S. aureus* to collagen **and** of displacing bacteria already bound to collagen. Once again, the present invention is not disclosed or suggested in the Hook PCT reference, and indeed provides significant and remarkable unexpected benefits not contemplated therein.

Accordingly, the Examiner's rejection on the basis of Hook PCT application WO 97/433314 is respectfully traversed and should be withdrawn.

One final rejection of the Examiner related to Claims 10, 13 and 16, but without addressing the merits of the rejections, Applicants have traversed this rejection through the cancellation of Claims 10 and 26 without prejudice, and the amendment of Claim 13 to adopt the Examiner's suggestions.

In light of the amendments and arguments as set forth above, and the attachments hereto, Applicants respectfully submit the present application has been placed in condition for allowance, and such action is earnestly solicited.

END OF REMARKS